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By: _____ Printed: ~~Margaret M. Hasson~~ D. Ellis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Coleman et al.

Title: A C5a-LIKE SEVEN TRANSMEMBRANE RECEPTOR

Serial No.:	08/462,355	Filing Date:	June 05, 1995
Examiner:	Ulm, J.	Group Art Unit:	1646

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REPLY BRIEF

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated December 31, 2002 ("the Examiner's Answer") in the above-identified application.

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of the claims on appeal under 35 U.S.C. § 101 on the grounds that the claimed polynucleotides allegedly do not possess "apparent or disclosed specific and substantial credible utility" (Examiner's Answer, page 4); and

(2) maintained the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because of the invention's alleged lack of utility.

I. Comment on the Appeal Brief's "Summary of Invention"

Appellants acknowledge the Examiner's objection to the "Summary of Invention" in Appellants'

Appeal Brief for allegedly being "deficient." (Examiner's Answer, page 3.) However, Appellants do not agree.

II. UTILITY REJECTION

A. Introduction

The Examiner's Answer states that "[t]here is neither evidence of record nor an assertion in the instant specification that the protein encoded by the claimed nucleic acid is a receptor for C5a. The instant application does not disclose a specific biological role for this protein." (Examiner's Answer, page 4.)

Nothing in the law requires Appellants to prove biological role or function, and the Examiner does not point to anything in the law suggesting such a requirement. Indeed, the only law on point is to the contrary: it is settled law -- and the Examiner does not rebut this -- that how an invention works (that is, its function) is utterly irrelevant to the utility analysis. In short, the entirety of the Examiner's argument is based on the confusion between, and improper equation of, use and function.

In this case, Appellants have identified the claimed polynucleotides by association in a defined and narrow group: polynucleotides encoding C5a-like seven transmembrane receptors as well as expressed human polynucleotides. As demonstrated below and in the Appeal Brief, because polynucleotides encoding C5a-like seven transmembrane receptors as well as expressed human polynucleotides are predominantly useful, Appellants can state with great confidence that the claimed invention is useful. How the invention actually works is utterly irrelevant to the analysis.

B. Responses to Specific Arguments by Examiner

1. Biological function is irrelevant to utility

The Examiner states that "[t]he instant claims are drawn to an isolated nucleic acid defined sole [*sic*] by the fact that it encodes a protein, which, as yet, is of undetermined function or biological significance" and that "[t]here is little doubt that, after complete characterization, this protein and an isolated nucleic acid encoding it may be found it have a specific and substantial credible utility." (Examiner's Answer, pages 4 and 5.) However, Appellants have demonstrated a utility for the claimed

polynucleotides irrespective of whether or not a person would wish to perform additional experimentation on biological function as another utility. The fact that additional experimentation could be performed to determine the functionality of the claimed polynucleotides or their encoded polypeptides does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the specific function of the claimed polynucleotides or their encoded polypeptides. Once again the Examiner confuses use with function.

2. Drug screening is a specific, substantial and credible utility

The Examiner argues that "[e]ven if the expression of Appellant's individual protein is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed antibody[1] has no 'well-established' use." (Examiner's Answer, page 8.)

Contrary to the Examiner's allegation, there is indeed a "specific and substantial" interpretation for the results of drug screening and toxicology testing using the claimed polynucleotides. Monitoring the expression of the claimed polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide (or its encoded polypeptide) is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects that may limit its usefulness as a specific drug. Learning this from an array in a gene expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

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[1]The Examiner in the quoted sentence refers to "the individually claimed antibody." Appellants further note that the Examiner referred on page 7 of the Examiner's Answer to "those polypeptides which are bound by the antibodies encompassed by the instant claims." Appellants note that the claims on appeal are directed to polynucleotides and assume that the Examiner's references to the "claimed antibody" and the "antibodies encompassed by the instant claims" were made inadvertently.

However, the Examiner continues to view the utility of the claimed polynucleotides in toxicology testing and drug screening as requiring knowledge of either the biological function or disease association of the polynucleotides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides or their encoded polypeptides, alleging that "Applicant has failed to identify the consequences of identifying a compound which is toxic to a polypeptide encoded by the claimed polynucleotide." (Examiner's Answer, page 7.). The Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides or their encoded polypeptides, but to other polynucleotides or polypeptides. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the claimed polynucleotides or their encoded polypeptides, and is a specific, substantial and credible utility.

The Examiner provides neither evidence nor sound scientific reasoning, only unsupported personal opinion, to support the allegation that knowledge of "biological significance" or "disease association" is required for toxicology testing and drug screening.

3. Irrelevance of disease association to utility in toxicology testing

The Examiner asserts that the specification does not disclose an association of the polypeptides encoded by the claimed polynucleotides with "even a single disease or disorder," and therefore that "[t]he artisan is required to perform substantial further experimentation on the claimed material itself in order to determine to what 'practical use' any expression information regarding this polynucleotide could be put." (Examiner's Answer, page 8.)

These are irrelevant. Appellants need not demonstrate whether the claimed polynucleotides are associated with disease. Appellants need only demonstrate that the claimed polynucleotides are useful.

The claimed polynucleotides can be used for toxicology testing in drug discovery without any knowledge of disease association. Monitoring the expression of the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or its encoded polypeptide, regardless of the disease association of the claimed

polynucleotides. The claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides or their encoded polypeptides, regardless of any possible utility for measuring the properties of the claimed polynucleotides.

4. Discussion of toxicology testing in the Specification

The Examiner alleges that "toxicology testing and drug discovery are not specifically recited in the specification as originally filed" and that "the particulars of toxicology testing with SEQ ID NO:2 are not disclosed in the instant specification." (Examiner's Answer, pages 6 and 7.) Well-established utilities, such as toxicology testing, need not be explicitly disclosed in a patent application. Furthermore, the Examiner's position amounts to nothing more than the Examiner's disagreement with Appellants' assertions about the knowledge of a person of ordinary skill. The Examiner must accept Appellants' assertions to be true. The Examiner's Answer fails to address the disclosure in the instant specification on gene and protein expression monitoring applications, as discussed below.

Support for the utility of the claimed polynucleotides in toxicology testing, as well as for utility in drug screening, may be found in the specification. For example,

> Because CALR is specifically expressed in cells active in immunity, the nucleic acid (calr), polypeptide (CALR) and antibodies to CALR are useful in investigations of and interventions in the normal and abnormal physiologic and pathologic processes which comprise the mast cell's role in immunity. Therefore, an assay for upregulated expression of CALR can accelerate diagnosis and proper treatment of conditions caused by abnormal signal transduction due to anaphylactic or hypersensitive responses, systemic and local infections, traumatic and other tissue damage, hereditary or environmental diseases associated with hypertension, carcinomas, and other physiologic or pathologic problems.
>
> The nucleotide sequence encoding CALR (or its complement) has numerous other applications in techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes for Southerns or northerns, use as oligomers for PCR, use for chromosomal and gene mapping, use in the recombinant production of CALR, use in generation of anti-sense DNA or RNA, their chemical analogs and the like, and use in production of chimeric molecules for selecting agonists, inhibitors or antagonists for design of domain-specific therapeutic molecules. (Coleman '355 application, page 6, lines 15-29.)

The Coleman '355 application further teaches that:

> The nucleotide sequence can be used to develop an assay to detect activation, inflammation, or disease associated with abnormal levels of CALR expression. The nucleotide sequence can be labeled by methods known in the art and added to a fluid or tissue sample from a patient. After an incubation period sufficient to effect hybridization, the sample is washed with a compatible fluid which contains a visible marker, a dye or other appropriate molecule(s), if the nucleotide has been labeled with an enzyme. After the compatible fluid is rinsed off, the dye is quantitated and compared with a standard. If the amount of dye is significantly elevated (or lowered, as the case may be), the nucleotide sequence has hybridized with the sample, and the assay indicates an abnormal condition such as inflammation or disease. (Coleman '355 application at page 9, lines 13-22.)

5. Utility of all expressed polynucleotides in toxicology testing

The Examiner asserts that use as a control for toxicology testing is not specific and substantial, and therefore not well-established, because it "would apply to virtually every member of a general class of materials, such as any collection of proteins or DNAs, but, it is not a specific utility with respect to SEQ ID NO:2." (Examiner's Answer, page 7.) The Examiner does not point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of polypeptides or polynucleotides can be so used, then they all have utility. The issue is, once again, whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities presupposes that many different inventions can have the exact same utility. If the Examiner's argument was correct, there could never be a well established utility, because you could always find a generic group with the same utility!

Furthermore, the Examiner is incorrect in stating that "virtually every member of a general class of materials, such as any collection of proteins or DNAs" could be used in toxicology testing. (Examiner's Answer, page 7.) The property of the claimed polynucleotides that makes them useful as controls for toxicology testing is their expression in naturally occurring cells. A polynucleotide having a random, non-naturally occurring sequence would most likely not be useful as a control for toxicology testing.

The Examiner further asserts that "the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array" and that this is, again, a general utility. (Examiner's Answer, page 8.) Appellants note that while the information derived from an array does depend upon the pattern derived from individual members of the array, an array still cannot be made without individual members. Thus each individual naturally-occurring polynucleotide sequence has a utility in creating arrays. Each of these individual polynucleotide sequences has a unique and specific utility in that it records the expression level of a unique gene. This is a substantial, "real world" utility in that one of ordinary skill in the art would know how to use the sequences of the claimed polynucleotides in an array, without any further experimentation.

C. The Examiner's Answer is Based on Flawed Assumptions about the Legal Standard for Utility

In the face of Appellants' demonstration of numerous disclosed and well-established utilities for the claimed polynucleotides, the Examiner's Answer does not offer any facts or sound scientific reasoning as would be required to overcome the presumption of utility that must be attributed to the claimed invention as a matter of law. For example, the Examiner's Answer has no answer for the disclosed utilities of the claimed polynucleotides in gene expression monitoring applications that are discussed in the Appeal Brief.

The Examiner has not and cannot provide **any** evidence tending to show that a person of ordinary skill in the art could not achieve the disclosed utilities, or indeed that any experimentation whatsoever would be required to put the claimed invention to beneficial use. And the Examiner's Answer utterly fails to address the Appellants' overwhelming evidence demonstrating not only that persons of ordinary skill in the art recognize the utility of inventions such as those claimed, but also that the likelihood that the claimed invention would achieve those utilities is far beyond substantial.

Apart from ignoring the presumption of utility and the Examiner's burden to overcome it, the entirety of the Examiner's Answer ultimately is based on three flawed assumptions. They are:

i. the claimed invention cannot be proven to be useful until the biological roles or functions of the claimed polynucleotides also are proven;

ii. assignment to a family whose members are known to be useful does not establish utility unless the members share a single, common utility; and,

iii. the *Brenner* v. *Manson* case somehow supports the Examiner's position in the present situation.

All of these assumptions are incorrect.[2]

1. <u>The precise biological role or function of an expressed polynucleotide or polypeptide is not required to demonstrate utility</u>

Rather than responding to Appellants' evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not specific, substantial, and well-established utilities (Examiner's Answer at pages 7-8). The Examiner is incorrect both as a matter of law and as a matter of fact.

The basis of the Examiner's argument is that, without information as to the precise biological role of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polynucleotides to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide an "interpretation for the result" generated in any given expression analysis (Examiner's Answer, page 8).

It may be that such "interpretations" and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not,

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[2] It is respectfully submitted that the entirety of the Examiner's alleged rebuttal of Appellants' arguments and reasoning in the Examiner's Answer are based on these three incorrect assumptions. Nevertheless, to the extent that Appellants do not specifically rebut these points on a line-by-line basis, this is not to be construed as acquiescence to their veracity, and Appellants do not waive the right to rebut them individually at any later point in the proceedings.

as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999)[3]. If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt that the present invention easily meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

Biological role or function is, instead, merely one factor that can be relevant in demonstrating whether there is a "substantial likelihood" a claimed invention can achieve the identified benefits. It may be particularly helpful in those cases where it is necessary to prove that the identifiable benefit of one biological composition can be imputed to another. In these cases, see, *e.g.*, *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995), because there is no direct evidence that the

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[3] *Juicy Whip* states:
An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

biological composition can achieve any given utility, knowledge of biological function can be used to prove a "substantial likelihood' of utility indirectly, by association. Biological function serves as a link between a compound whose utility otherwise would be unknown and another compound having known utility. If, for example, a prior art biological composition is known to be a target in the treatment of disease, one way the applicant can prove utility is by demonstrating that the claimed invention is substantially likely to share the utility for disease treatment because it also shares a biological role with the prior art composition.

But in other cases, such as this one, proof of biological function is not necessary. In those cases, the evidence already is sufficient to show that there is a substantial likelihood that the claimed invention produces the alleged benefit. The claimed invention has a known utility whether or not it can be linked (through biological function) with some other composition.

By implicitly requiring knowledge of biological function for any claimed polynucleotide or polypeptide, the Examiner has, contrary to law, elevated what has long been acknowledged to be an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Assignment to a family whose members are useful establishes utility

For the reasons discussed in Section III.B. of the Appeal Brief, the Examiner cannot properly impose a "common utility" requirement with respect to the C5a-like seven transmembrane receptor family (and the family of expressed polypeptides) to which the CALR encoded by the claimed polynucleotides belongs. The Examiner's attempt to do so, if permitted to succeed, would improperly raise the threshold of patentable utility for biotechnological inventions to a point above that of other classes of inventions.

3. The Examiner's reliance on *Brenner* v. *Manson* is misplaced

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention

is disclosed in the Coleman '355 application to be useful as a tool in a number of gene expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function of the claimed polynucleotides is superfluous information for the purposes of establishing utility.

The fact that the claimed invention already has a disclosed use as a tool in then available technology distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, *Brenner* v. *Manson*, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect.

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the SEQ ID NO:1 polynucleotide is an expressed polynucleotide that was disclosed to be useful in the Coleman '355 application for many known applications involving gene expression analysis. Its utility is not a matter of guesswork. It is not a random DNA or polypeptide sequence that might or might not be useful as a scientific tool. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which

belongs to a class of molecules containing a significant number of useless compositions.[4]

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug.

Accordingly, in this case, biological function is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the evidence presented by the Appellants demonstrates. Given that the claimed invention has disclosed and well-established utilities, the Appellants need not demonstrate utility by imputation.

In the end, the Examiner has failed to recognize that new technologies have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polypeptide or polynucleotide could be usefully employed without further research. It has created a need for new tools, such as the claimed polynucleotides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

III. ENABLEMENT REJECTION

The rejection set forth in the Examiner's Answer is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

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[4] While not necessary to reverse the Examiner's rejections, it is appropriate to point out that because the SEQ ID NO:1 polynucleotide is an expressed human polynucleotide, it is highly more likely than not that it belongs to the class of molecules that have been pre-selected by nature to be useful.

IV. CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: February 26, 2003

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